

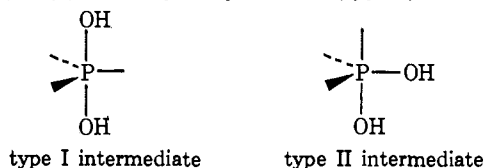
Kinetic Studies of Oxygen-18 Exchange of Geometrically Constrained Phosphine Oxides. Stereomutation at Pentacoordinated Phosphorus¹

Ronald B. Wetzel and George L. Kenyon*²

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720, and the Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143. Received August 24, 1973

Abstract: The kinetics of oxygen-18 exchange of a series of phosphine oxides, 1-phosphabicyclo[2.2.1]heptane 1-oxide (1), 1-phosphabicyclo[2.2.2]octane 1-oxide (2), 1-ethyl-2,2,3-trimethylphosphetane 1-oxide (3), 1-ethylphospholane 1-oxide (4), 1-ethylphosphorinane 1-oxide (5), and triethylphosphine oxide (6), were measured under a variety of conditions. Exchange presumably proceeds in each case through dihydroxyphosphoranes of trigonal-bipyramidal geometry. It was found that pH-rate profiles and Bunnett plots may be used as criteria for distinguishing between exchange mechanisms proceeding *via* dihydroxyphosphoranes in which both oxo ligands are apical (type I intermediates) and dihydroxyphosphoranes in which the oxo ligands are situated apical-equatorial (type II intermediates). Compounds 4, 5, and 6 were found to exchange by way of type I intermediates and compounds 1 and 3 by type II intermediates. A type I intermediate for phospholane 4 was unexpected, since this requires diequatorial placement of the five-membered ring. Compound 2 underwent exchange much more slowly than the other phosphine oxides, presumably because of the unfavorable electronic effect of forming the type II intermediate, which in this case was not compensated for by relief of ring strain in going into the transition state. Relief of ring strain in 1 and 3 facilitated formation of the type II intermediates. By a simple Berry pseudorotation mechanism the type II intermediate of 1 would not be expected to undergo facile ligand interchange. Since 1 readily underwent exchange, other mechanistic interpretations are considered.

Oxygen-18 exchange in phosphine oxides by attack of water is presumed to involve pentacoordinated phosphorus intermediates of trigonal-bipyramidal geometries.³⁻⁵ When backside attack is allowed, this process can proceed, in analogy to S_N2 displacements at carbon, with net inversion of configuration, *via* a trigonal-bipyramidal intermediate with both entering and leaving oxygens in apical positions (type I).^{4,5} In other



cases, because of built-in geometrical constraints, the entering and leaving oxygens are denied such a diaxial arrangement. In these situations, since the attacking water is presumed to enter in an apical position, the phosphoryl oxygen is forced to occupy an equatorial position (type II).³ In order for this phosphoryl oxygen to occupy an apical leaving position, some mode of ligand interchange is required. The most widely accepted mechanism for such a stereomutation, or positional interchange, at pentacoordinated phosphorus is fundamentally that proposed by Berry,⁶ called Berry pseudorotation (BPR).⁷ Ugi, Ramirez, and coworkers⁸

have proposed an alternative mechanism to account for these stereomutations called turnstile rotation (TR).⁹

In the previous paper,¹⁰ we described the syntheses of a series of bicyclic and monocyclic phosphine oxides 1-5. Some of these compounds are so geometrically constrained that they can form only type II intermediates. On the other hand, since more electronegative atoms tend to prefer the apical positions in a trigonal bipyramid,¹¹ at least the acyclic triethylphosphine oxide 6 was anticipated to undergo oxygen-18 exchange *via* the type I intermediate.

In this paper we describe the oxygen exchange kinetics, in acidic, neutral, and basic aqueous solution, of phosphine oxides 1-6. We were able to distinguish between intermediates of type I and II by the shapes of the pH-rate profiles. Possible modes of stereomutation of phosphoranes derived from the highly geometrically constrained 1-phosphabicyclo[2.2.1]heptane 1-oxide (1) are presented.

Results and Discussion

Rates of oxygen exchange under a variety of conditions for compounds 1-6 were determined. Figure 1

(1) Presented in part at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 26-31, 1973.

(2) Address correspondence to this author to the Department of Pharmaceutical Chemistry, University of California, San Francisco, Calif. 94143.

(3) D. G. Gorenstein, *J. Amer. Chem. Soc.*, **94**, 2808 (1972).

(4) L. Horner and H. Winkler, *Tetrahedron Lett.*, 3271 (1964).

(5) D. B. Denney, A. Tsolis, and K. Mislow, *J. Amer. Chem. Soc.*, **86**, 4486 (1964).

(6) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(7) In a Berry pseudorotation, an equatorial substituent in the trigonal bipyramid is chosen as a pivot and the other apical and equatorial substituents interchange positions pairwise with respect to the pivot, proceeding *via* a tetragonal-pyramidal transition state (or intermediate) with the pivot at the apex.

(8) (a) I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *Accounts Chem. Res.*, **4**, 288 (1971); (b) F. Ramirez, S. Pfohl, E. A. Tsolis, J. F. Pilot, C. P. Smith, I. Ugi, D. Marquarding, P. Gillespie, and P. Hoffmann, *Phosphorus*, **1**, 1 (1971); (c) I. Ugi, D. Marquarding, H. Klusacek, G. Gokel, and P. Gillespie, *Angew. Chem., Int. Ed. Engl.*, **9**, 703 (1970); (d) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *ibid.*, **10**, 687 (1971); (e) I. Ugi and F. Ramirez, *Chem. Brit.*, **8**, 198 (1972); (f) F. Ramirez and I. Ugi, *Advan. Phys. Org. Chem.*, **9**, 25 (1971).

(9) In a turnstile rotation, the five ligands around pentacoordinated phosphorus, by undergoing slight but significant angular distortions, divide themselves into two sets, a trio and a pair. In this case stereomutation is postulated to occur by mutual counterrotation of these two sets with subsequent collapse to a new trigonal bipyramid.

(10) R. B. Wetzel and G. L. Kenyon, *J. Amer. Chem. Soc.*, **96**, 5189 (1974).

(11) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).

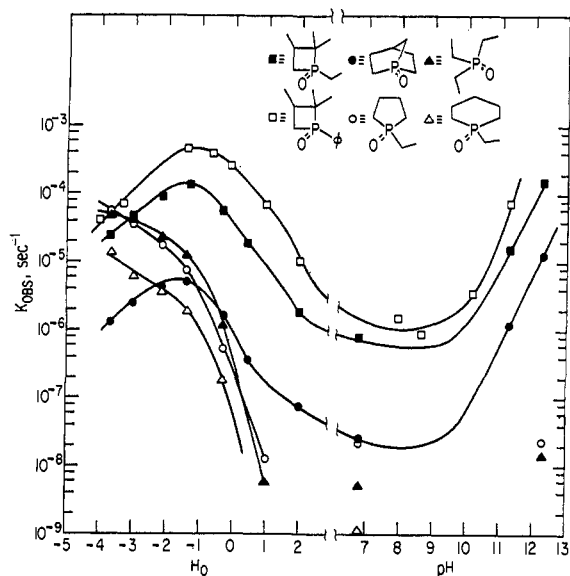
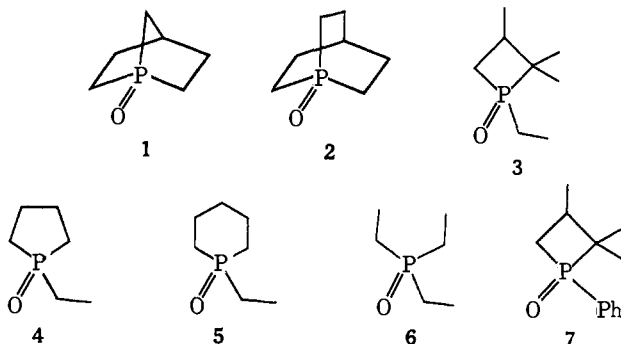


Figure 1. pH-rate profiles for the ^{18}O exchange of the phosphine oxides shown. The observed rate constants were either measured at or extrapolated to 101° . The profile shown for compound 7 is from Gorenstein.³ Data are given in an Appendix, available in the microfilm edition of the Journal.

shows the pH-rate profiles at 101° for oxygen exchange of compounds 1 and 3–6, as well as the profile obtained by Gorenstein³ for 1-phenyl-2,2,3-trimethylphosphorane 1-oxide (7) (see paragraph at end of paper



regarding supplementary material). Some of these rate constants, more conveniently determined at higher temperatures, were extrapolated to 101° . Rate constants were determined following the general procedure of Gorenstein. That is, rates were followed by monitoring changes in $\text{P}=\text{O}$ stretching frequencies in the infrared. The reliability of this infrared technique was checked for each compound by following the kinetics of selected runs by mass spectrometry. Within the error of the mass spectral measurements, the observed rate constants were the same by both methods. By the infrared method even compound 1, with the most complex set of Fermi resonance bands in the phosphoryl region,¹⁰ gave excellent least-squares fits in its linear first-order kinetic plots with a correlation coefficient of 0.9974.

There is no entry in Figure 1 for compound 2. This compound underwent oxygen exchange with extreme reluctance, such that even after months of heating at 101° only a small amount of ^{18}O incorporation ($<3\%$) could be detected by mass spectrometry. Similarly, heating at 152° for 1 month in 2 N HCl failed to give significant exchange.

The pH-rate profiles can be readily divided into two groups. The phosphine oxides in one group (1, 3, and 7) each exhibit a rate maximum in strong acid (about 4 N). In addition, these compounds' rates are dramatically enhanced by KOH concentration. The other group of profiles, those for compounds 4, 5, and 6, exhibits steadily increasing rates with increasing concentration of HCl , up to 10 N HCl in each case. Additionally, there seems to be no significant basic catalysis in this series. These latter compounds presumably exchange *via* type I intermediates (see below).

The compounds which display the rate maximum in strong acid possess two striking common features. One, they all must give intermediate phosphoranes in which one of the two hydroxy ligands is in an equatorial position. That is, they all must give type II intermediates. Since the three phosphorus-carbon bonds in 1 cannot become coplanar in a phosphorane, one of the three alkyl substituents must be placed apically and, consequently, one of the generally apicophilic hydroxy ligands equatorially. Ring strain in 3 and 7, which precludes diequatorial placement of the four-membered ring (as demonstrated by Gorenstein's observation that epimerization of 7 occurs at a much slower rate than exchange), likewise places one of the hydroxy ligands equatorial in phosphorane intermediates derived from these compounds. The second feature, which is a consequence of the first, is that intermediate phosphoranes of 1, 3, and 7 must undergo stereomutation in order for oxygen exchange to occur. This is due to the requirement of apical attack and apical leaving, a widely accepted concept which has received experimental support in stereochemical studies of Mislow,¹² Marsi,¹³ Westheimer,¹⁴ and DeBruin.¹⁵ It should be noted, however, that if equatorial attack and equatorial leaving be postulated, similar mechanistic conclusions to those discussed later can still be drawn.

Exchange in Acidic Solutions.¹⁶ How can we account for the two ways that phosphine oxide exchange responds to acid catalysis? Does it lie in the fact that one group must undergo stereomutation while the other does not? Or is it a consequence of the different

(12) K. Mislow, *Accounts Chem. Res.*, **3**, 321 (1970).

(13) (a) K. L. Marsi, *J. Amer. Chem. Soc.*, **91**, 4724 (1969); (b) K. L. Marsi and R. T. Clark, *ibid.*, **92**, 3791 (1970); (c) K. L. Marsi, *ibid.*, **93**, 6341 (1971); (d) K. L. Marsi and J. E. Oberlander, *ibid.*, **95**, 200 (1973).

(14) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

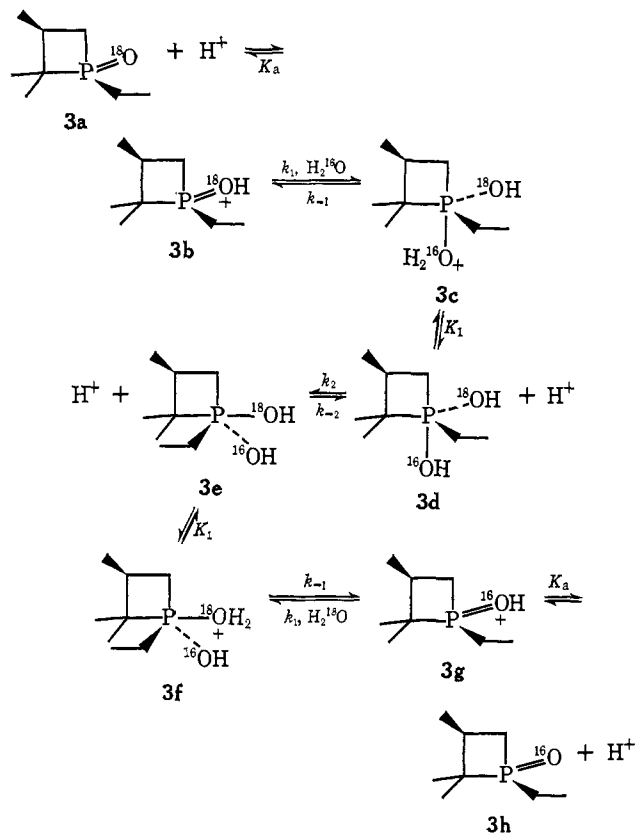
(15) (a) K. E. DeBruin and D. M. Johnson, *J. Amer. Chem. Soc.*, **95**, 4675 (1973); (b) K. E. DeBruin, A. D. Padilla, and M. T. Campbell, *ibid.*, **95**, 4681 (1973).

(16) One aspect of the kinetics of oxygen exchange in aqueous acid, which will not be further discussed, is the apparent existence in even weakly acidic solution of very strong complexes between the trialkylphosphine oxides used in this study and HCl . This complex formation was so strong that a (weakly basic) phosphine oxide in aqueous solution was able to liberate free trimethylamine from trimethylamine hydrochloride (Wetzel and Kenyon, unpublished results). Hydrogen-bonded complexes of this sort are known to exist between oxo bases and protic molecules of all sorts [D. Hadzi, C. Klöfutar, and S. Oblak, *J. Chem. Soc. A*, 905 (1968)], but trialkylphosphine oxides seem to give by far the most stable complexes [G. Aksnes, *Acta Chem. Scand.*, **14**, 1475 (1960); G. Aksnes and T. Gramstad, *ibid.*, **14**, 1485 (1960)]. Aksnes has discussed the kinetics of acid-catalyzed hydrolysis of phosphites and phosphates in terms of this hydrogen-bonding ability of the phosphoryl group [G. Aksnes, *Acta Chem. Scand.*, **14**, 1526 (1960)], concluding that catalysis occurs primarily *via* hydrogen bonding rather than direct protonation of substrate. While this may be a factor in the dilute acid-neutral region of Figure 1, where the profiles of some of the less reactive phosphine oxides are not smooth, it appears likely that catalysis in the strong acid region is proceeding *via* complete protonation (see, in particular, the discussion on Bunnett plots).

stereochemistries of the intermediates, diapical hydroxy ligands in **4**, **5**, and **6** and apical-equatorial hydroxy ligands in **1**, **3**, and **7**?

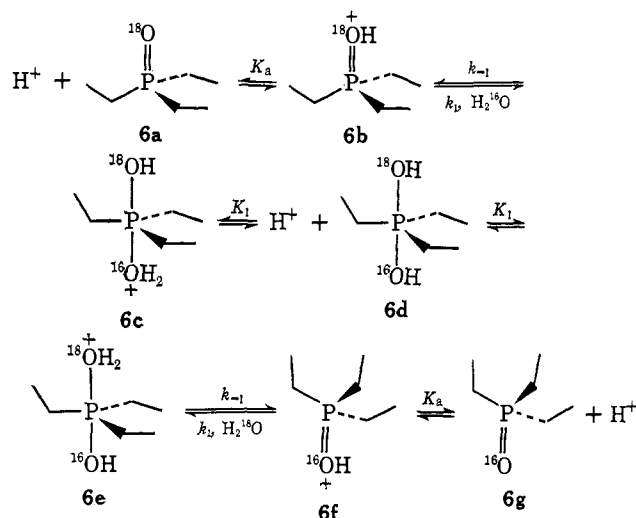
Scheme I was prepared, based on a similar scheme of

Scheme I



Gorenstein, to summarize the probable mechanism of oxygen exchange for compounds which give type II intermediates. Scheme II summarizes the probable

Scheme II



mechanism for those compounds which give type I intermediates. The essential difference between Schemes I and II is that there is no stereomutation step in Scheme II.

Several observations suggest that all the compounds studied show rate-limiting hydration and that therefore compounds **1**, **3**, and **7** are not showing rate-limiting stereomutation. If the rate-limiting steps differed in

the two schemes, it might be expected that entropies of activation of **4**, **5**, and **6** would differ substantially from those of **1**, **3**, and **7**. Rate-limiting hydration, involving the collision of water with phosphine oxide to form an activated complex (with concomitant loss of translational freedom of 1 mol of water), would predict for compounds **4**, **5**, and **6** an entropy of activation of -20 to -30 eu, in analogy to acid-catalyzed hydrolysis of esters of carboxylic acids.¹⁷ Rate-limiting stereomutation, presumably involving only minor changes in vibrational and rotational degrees of freedom of the pentacoordinate intermediate, would lead to entropies of activation near zero for **1**, **3**, and **7**.

The thermodynamic parameters for the exchange reaction in 6 *N* HCl of phosphine oxides **1** and **3-6** are listed in Table I. There is no great difference in the

Table I. Activation Parameters

Compd	Medium	ΔH^\ddagger , kcal/mol	ΔS^\ddagger , cal/(deg mol)
1	6.00 <i>N</i> HCl	24 ± 1.1	-23 ± 3
3	6.00 <i>N</i> HCl	20 ± 0.8	-28 ± 2
4	6.00 <i>N</i> HCl	22.8 ± 0.4	-23 ± 1
5	6.00 <i>N</i> HCl	24 ± 1.2	-23 ± 3
6	6.00 <i>N</i> HCl	23 ± 1.3	-22 ± 4
1	0.05 <i>N</i> phosphate	28.3 ± 0.5	-17 ± 1
1	1.00 <i>N</i> KOH	22 ± 1.4	-24 ± 4
3	0.05 <i>N</i> phosphate	25.7 ± 0.7	-18 ± 2
3	1.00 <i>N</i> KOH	20.4 ± 0.7	-22 ± 2

entropies of activation; all are between -20 and -30 eu, consistent with a bimolecular rate-determining step for each.

Solvent isotope effects at 0.475 *N* HCl (or DCl) were determined for each compound. While rate-limiting hydration might be expected to give a small isotope effect due to hybridization changes in water before and after bond formation to phosphorus, rate-limiting stereomutation would be expected to show no dependence on the isotope of hydrogen in solvent and on the oxo ligands. Table II shows that only compound **3**

Table II. Solvent-Isotope Effects (0.475 *N* HCl, 3.5 *N* KCl, 101°)

Compd	k_{H_2O}/k_{D_2O}
1	0.98 ± 0.06
3	1.4 ± 0.2
4	0.95 ± 0.2
5	0.90 ± 0.07
6	0.98 ± 0.08

gave a k_{H_2O}/k_{D_2O} greater than 1.0. The other compounds gave values which are within experimental error of 1.0, with the exception of compound **5**, which gave a value which is clearly less than 1.0. It can be seen that the solvent-isotope effects correlate well with the observed rates of exchange for these compounds at 0.475 *N* HCl; that is, the most reactive phosphine oxide at this acid concentration exhibits the highest k_{H_2O}/k_{D_2O} and the least reactive oxide the lowest k_{H_2O}/k_{D_2O} . The effects do not fall into families similar to those defined by pH-rate profiles. These results also indicate a common rate-determining step for this series in acid.

(17) L. L. Schalegar and F. A. Long, *Advan. Phys. Org. Chem.*, **3**, 25 (1963).

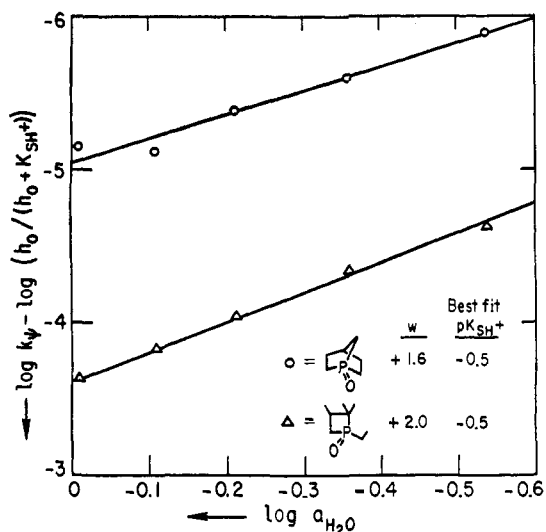


Figure 2. Bunnett plots (see text) for compounds 1 and 3 in the strong acid region. pK_{SH^+} values of -0.5 were assumed in each case to maximize linearity.

The other possible explanation for the two ways that phosphine oxide oxygen exchange responds to acid catalysis is that there is some critical difference in the stereochemistries of the phosphorane intermediates. Gorenstein has attributed the rate maximum observed for 7 to a decrease in the activity of water as acidity increases. It seemed possible that, because the substitution pattern with respect to oxo ligands in intermediate phosphorane derived from 1, 3, and 7 differs from the pattern in intermediates of 4, 5, and 6, some aspect of water activity might be affecting stabilities of intermediates to different extents.

The different acid-catalysis behaviors of the phosphine oxides can be formalized by preparing Bunnett plots¹⁸ for each compound. Using the rates obtained at acid concentrations of 0.475 *N* and higher, the log of the observed rate constant was plotted *vs.* the log of the activity of water at each acid concentration.

Since phosphine oxides have an appreciable basicity, it was important to include consideration of the pK_a of the conjugate acid in the Bunnett plots; that is, the observed rate constants had to be corrected for the amount of protonation of substrate at each acid concentration. Although a value of $pK_a = 0$ for trimethylphosphine oxide has been reported,¹⁹ it has recently been questioned by Haake.²⁰ Russian workers,²¹ using Haake's method for determining basicities of phosphoryl compounds, have recently reported a pK_a value for triethylphosphine oxide of -1.0 . Values for other trialkylphosphine oxides determined by these workers ranged from -1.5 to -2.5 . Basicities for the other compounds used in this study have not been reported. Gorenstein reports a value of -3 for compound 7,³ but this is not unreasonable since phenyl substitution seems generally to decrease basicity in phosphine oxides.²⁰

(18) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

(19) P. Nylén, *Z. Anorg. Allg. Chem.*, **246**, 227 (1941).

(20) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).

(21) N. K. Skvortsov, A. V. Dogadina, G. F. Tereschchenko, N. V. Morkovin, B. I. Ionin, and A. A. Petrov, *J. Gen. Chem. USSR*, **41**, 2839 (1971).

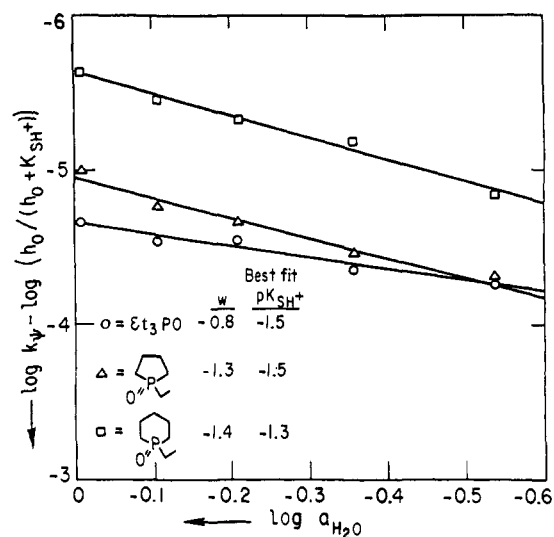


Figure 3. Bunnett plots (see text) for compounds 4, 5, and 6 in the strong acid region. pK_{SH^+} values of -1.3 , -1.5 and -1.5 , respectively, were assumed to maximize linearity.

Since only one of the compounds studied had a known pK_a , it was decided to choose the most linear of the Bunnett plots graphed for each compound over a whole range of basicities. In each case there was a particular value which gave a much more linear plot, and in each case that value differed from -1.0 by no more than 0.5 pK units. It should be noted that the alternative approach, which is to assign a pK_a of -1.0 for each compound, gives some nonlinearity in each case (which is not unusual in Bunnett plots) and w values which differ from those obtained in the best-fit method by only a few tenths. Furthermore, these slightly different w values serve to accentuate the trend to be discussed below,²² so it is felt that there is no harm, and perhaps some validity, in using the best-fit values.

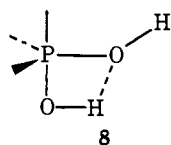
The two types of pH-rate profiles observed in Figure 1 are carried over into two distinct types of linear Bunnett plots (Figures 2 and 3), each of which falls into one of the three empirical mechanistic categories determined by Bunnett.¹⁸ Compounds 1 and 3 give w values ($+1.6$ and $+2.0$) which fall into the category of reactions in which water is involved as a nucleophile in the rate-determining step. The slight positive dependence of reaction rate on water activity, as shown by the Bunnett w values, confirms Gorenstein's rationale for the maximum in the exchange reaction of 7. The w values are thus consistent with the idea of a rate-determining attack of water on the protonated phosphine oxide and thus support the mechanistic conclusions reached independently on the basis of entropies of activation.

The w values for 4, 5, and 6 (Figure 3) are more difficult to rationalize. These compounds give values (-1.3 , -1.4 , and -0.8 , respectively) which indicate that rate is essentially independent of water activity, which confirms the conclusion one would make based on the pH-rate profiles in Figure 1. They fall well within the range of w values which, according to Bun-

(22) That is, those compounds with positive w values become more positive, and those with negative w values become more negative.

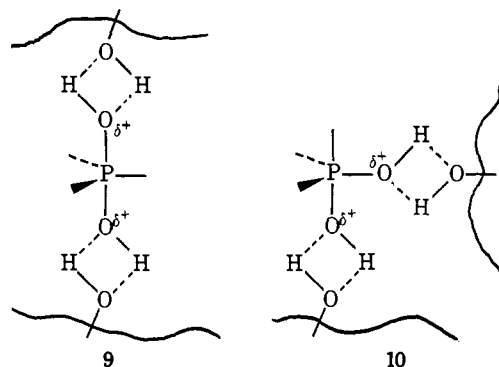
nett,¹⁸ indicate reactions in which water is not involved as a nucleophile. But it is difficult to conceive of a mechanism in which water is not involved, subsequent to protonation of the phosphine oxide, in the rate-determining step. Also, the entropies of activation of these compounds determined at 6 *N* HCl (after divergence in pH-rate profiles is well begun) are quite similar to those of **1** and **3**, suggesting a rate-determining step involving attack by water on the protonated phosphine oxide.

One approach to the unusual variation in *w* values is to consider changes in hydration between the intermediates in the two classes of compounds. Bunnett's theoretical justification of the meaning of *w* values is that they indicate *total* changes in hydration in going from substrate to activated complex, relative to the difference in hydration between a protonated and unprotonated Hammett base. If the total quantity of hydration is not changed from reactants to activated complex, a *w* value of 0 is expected, even if a molecule of water has been incorporated covalently into the substrate. If compounds **4**, **5**, and **6** for some reason require fewer waters of hydration in the activated complex than compounds **1** and **3**, the source of the difference in *w* values can be assigned. It is more likely, however, that phosphoranes derived from **1** and **3** should require fewer waters of hydration than the corresponding intermediate from **4**, **5**, and **6** given the obvious capacity for internal hydrogen bonding in the former (**8**). Hydration considerations thus fail to provide a good rationale.



It is possible to rationalize the apparent lack of dependence on water activity of compounds **4**, **5**, and **6** if one considers the nature of protic molecules in concentrated acid. Since water is involved in solvating protons, the availability of the electron pairs on the oxygen of water, which is the nucleophile in the oxygen exchange reaction, will decrease as the hydrogen ion concentration increases. If, as seems likely, proton transfers are rapid with respect to the hydration step, the transition state in the exchange reaction presumably closely resembles the symmetric intermediate **9**, in which phosphorus is apically bonded to two equivalent oxo ligands. These ligands are of substantially greater electronegativity than the hydroxy ligands of the corresponding intermediate in the neutral reaction, since the oxy ligands of **9** are intimately involved in the general solvation of hydrogen ions in strong acid solutions. This increase in the electronegativity of the apical ligands stabilizes the intermediate phosphorane.¹¹ Thus the decrease in water activity in strong acid is counterbalanced by a stabilization of the intermediate in strong acid, resulting in a deceptive *w* value.

While an intermediate (**10**) derived from **1** or **3** is similarly involved in the solvation of hydrogens ions, there is now a *destabilization* of the intermediate since one of the two oxo ligands of steadily increasing electronegativity is in the *equatorial* position. That is, not



only does the decrease in water activity in stronger acid solutions work against formation of these compounds, but the intermediate is destabilized as well.^{23, 25}

Exchange in Neutral and Basic Solutions. Compounds **1** and **3** continue to parallel the pH-rate profile found by Gorenstein for **7** in neutral and basic solutions, giving smooth curves of remarkable similarity. The acceleration observed in KOH solution is probably due to the relief of ring strain in these compounds plus the greater nucleophilicity of hydroxide ion compared to water. Thermodynamic parameters determined at pH 6.8 (25°) and in 1 *N* KOH are consistent with a bimolecular rate-determining step.

Compounds **4**, **5**, and **6** are generally much less reactive in neutral and basic media, although **4** shows about the same reactivity as **1** at pH 6.8. One can draw a rough line connecting the rate constants of **4** (as well as **5** and **6**) across the pH-rate profile until pH 1 is reached, indicating a general unresponsiveness to basic catalysis in these compounds. No totally satisfactory explanation has emerged to account for this behavior (see ref 26).

Phosphoranes and the Five-Membered Ring. Five-membered rings containing phosphorus (*e.g.*, **4**) are generally regarded²⁷ as possessing enough ring strain that they should behave similarly to **3** and **7**, giving a phosphorane with an apical-equatorial ring system and one equatorial and one apical hydroxy ligand. Nonetheless, there have been indications in the literature that, under certain circumstances, five-membered rings can

(23) In a recent discussion²⁴ of the application of Bunnett values to reactions of phosphorus compounds, it is suggested that trends in the pH-rate profiles may be due to the deviation of substrate and protonated substrate activities from the corresponding activities of the organic bases used to calibrate the H_0 function. While this may have something to do with the shapes observed in this study, it is difficult to see how it could affect the pH-rate profiles so differently. Recent work in which several nmr techniques were used to plot protonation curves for trialkylphosphine oxides indicates that the method used has a significant effect on how much like Hammett bases phosphine oxides appear to behave. But in all methods, the slope of a plot of $\log(BH^+/B)$ vs. H_0 was never more than 0.3 units from 1.0 (a "perfect" Hammett base).²¹

(24) P. Haake and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).

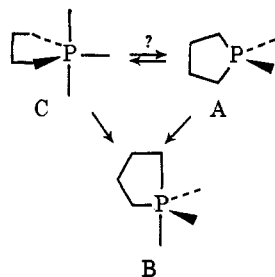
(25) It should be noted that, using the rate data and pK_a for **7** as determined by Gorenstein, a Bunnett plot gives a sweeping curve with an average *w* value of +5.5. If this average *w* value be indicative of mechanism, it suggests that water is involved in the rate-determining step in reactions of **7** as a proton-transfer agent, as Gorenstein suggested based on solvent isotope effects. Thus, **1**, **3**, and **7** may all show rate maxima because of a decrease in the activity of water, but to different degrees (as reflected in *w* values) and for different reasons. On the other hand, a best fit approach as described above gives a reasonably straight line at $pK_a = -0.5$, with a *w* value of +2.4, which would place it in the same category as compounds **1** and **3**.

(26) R. B. Wetzel, Ph.D. Dissertation, University of California, Berkeley, 1973.

(27) R. F. Hudson and C. Brown, *Accounts Chem. Res.*, **5**, 204 (1972).

be stable in a diequatorial arrangement.^{14,28-31} Thus, it was not totally unexpected that phosphorane **4** underwent oxygen exchange *via* a diequatorial five-membered ring. It was at first surprising, however, that **4** should react at essentially the same rate as acyclic **6**. The conventional wisdom concerning five-membered rings containing phosphorus can be summarized with the help of Scheme III. In equilibria between a phos-

Scheme III



phorane with a five-membered ring apical-equatorial (B) and a phosphorane with a five-membered ring diequatorial (C), or in reactions in which the A to C conversion *vs.* the A to B conversion is a clear choice, B predominates presumably due to a difference in ring strain between forms B and C.^{12-14,28,32,33} Reactions involving the conversion of a five-membered ring with tetrahedral phosphorus (A) to phosphorane intermediate B are greatly accelerated, again due to a release of ring strain.^{14,34,35} The relative energies of forms A and C have been less thoroughly studied, perhaps since it is more difficult to design experiments in which a process involving this energy difference, and *only* this energy difference, can be observed.

In fact, although the conversion of A to C is often spoken of as involving an increase in strain in the five-membered ring,^{12,14,27} there seems to be no data in the literature to verify such a statement. The relative rates of oxygen exchange of compounds **4** and **6** indicate that, in this system at least, there is not a big difference in strain energy between A and C.

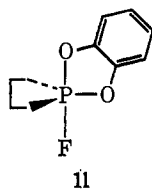
Further support for the diequatorial five-membered ring intermediate postulated for oxygen exchange of **4** lies in the reported epimerization rate of **12**. Marsi reported that both isomers of **12** undergo epimerization to an equilibrium mixture of isomers in refluxing con-

(28) E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963).

(29) W. Egan, G. Chauviere, K. Mislow, R. T. Clark, and K. L. Marsi, *J. Chem. Soc., Chem. Commun.*, 833 (1970).

(30) N. J. De'Ath, D. Z. Denney, D. B. Denney, and C. D. Hall, *Phosphorus*, in press; D. Z. Denney, D. W. White, and D. B. Denney, *J. Amer. Chem. Soc.*, **93**, 2066 (1971).

(31) Recent nmr studies of the phosphorane **11** are consistent with the structure shown, in which one of the five-membered rings is diequatorial [G. O. Doak and R. Schmutzler, *J. Chem. Soc. D*, 476 (1970)].

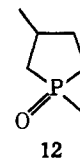
**11**

(32) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

(33) D. Gorenstein and F. H. Westheimer, *J. Amer. Chem. Soc.*, **92**, 634 (1970); D. Gorenstein, *ibid.*, **92**, 644 (1970).

(34) G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **19**, 931 (1965).

(35) S. E. Cremer, B. C. Trivedi, and F. L. Weil, *J. Org. Chem.*, **36**, 3226 (1971).

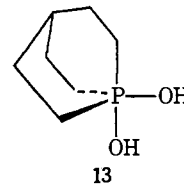
**12**

centrated hydrochloric acid in 2 hr.^{13a} Extrapolating the pH-rate profile of **4** to the H_0 of concentrated hydrochloric acid and correcting the rate obtained (101°) for the temperature of refluxing concentrated HCl, one obtains a half-life for oxygen exchange of **4** of *ca.* 1 hr. This implies essentially equal rates for epimerization and exchange for these very similar compounds which, as Gorenstein has suggested,³ further implies an "in-line" mechanism. This is to be compared with Gorenstein's study of **7**, which shows no epimerization at acid concentrations greater than *ca.* 4 N HCl, implying different pathways to exchange and epimerization.

Oxygen Exchange in 1-Phosphabicyclo[2.2.1]heptane 1-Oxide (1) and 1-Phosphabicyclo[2.2.2]octane 1-Oxide (2). By far the most surprising aspect of the kinetic results was the relative reactivities of compounds **1** and **2**. It had been expected that, if there were indeed any difference between the two compounds, it would be that **2** would undergo exchange more readily than **1**. Scheme IV summarizes the possible pathways for oxygen exchange in compound **1**. There are two possible trigonal-bipyramidal, pentacoordinated species derived from **1a**, namely **1b**, in which a six-membered ring is diequatorial, and **1e**, in which a five-membered ring is diequatorial. Any mechanism which depends on the transition from **1b** to **1e** will be disfavored by the inherent energy increase in placing a five-membered ring diequatorial from apical-equatorial (B to C in Scheme III). In a similar scheme involving compound **2**, all phosphorane intermediates are of equal energy since only six-membered rings are involved.

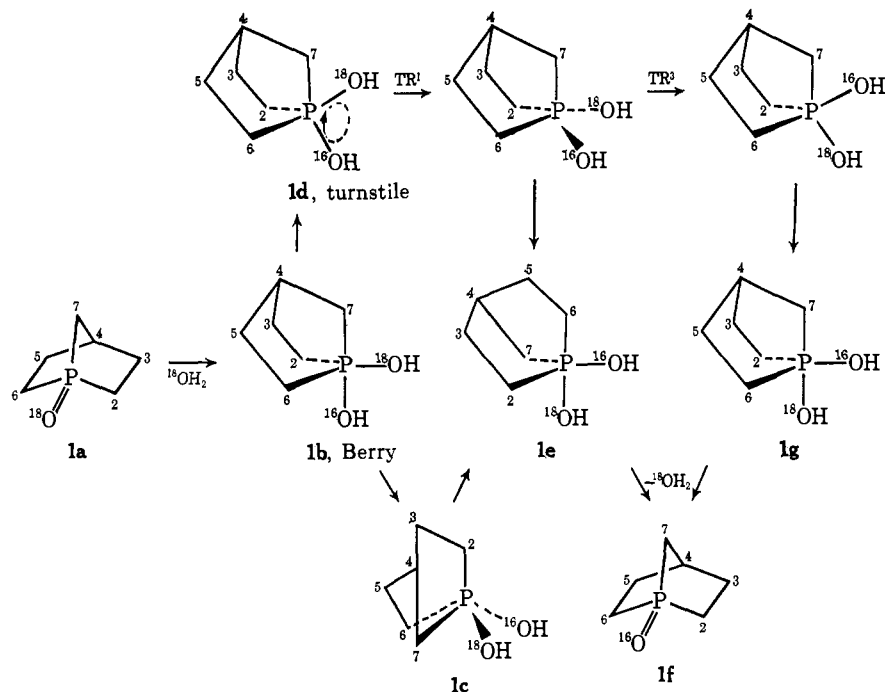
When these oxygen-exchange studies were designed, the expectation was that **1** would undergo exchange sluggishly compared to **2**, since the conversion **1b** to **1e** was likely to be disfavored with respect to the parallel conversion in oxygen exchange of **2**. In fact, not only was **1** found to be more reactive than **2**, but the difference in rates was remarkable. At an acid concentration at which all the other phosphine oxides, including **1**, exchanged completely in several days, compound **2** incorporated only a trace of oxygen from water after 3 months.

This difference appears to be due to the relative rates of formation of the phosphorane intermediate, as controlled by strain and electronic effects. Both **1** and **2** give intermediates (**1b** and **13**, respectively) in which one

**13**

alkyl substituent is situated unfavorably apical and one hydroxy ligand unfavorably equatorial. Compound **1** presumably overcomes this extra energy requirement in the same manner as **3** and **7**; relief of strain going from phosphine oxide to phosphorane. Examination of a molecular model of **1** shows considerable strain, which

Scheme IV



is absent in **2**. Phosphoranes **1b** and **13** are both essentially strain-free.³⁶ Compound **2** is therefore at a disadvantage in not possessing a well of strain energy which could contribute to the hydration step.

While the low reactivity of **2** compared to **1** can be explained in terms of commonly accepted criteria, there was no obvious explanation for why **1**, given its built-in resistance to BPR, exchanges at all. There is an obvious limitation in using the oxygen-exchange results for compound **1** to discuss modes of stereomutation of the presumed intermediate dihydroxyphosphorane. The pH-rate profiles shown in Figure 1 are reflective of relative rates of formation of the dihydroxyphosphoranes, and do not in themselves give information about relative energies of stereomutation of intermediates (in those cases in which stereomutation is implicated). Indeed, these kinetics are equally consistent with any ¹⁸O exchange mechanism which goes through a dihydroxyphosphorane intermediate formed in the rate-limiting step.

Space limitations preclude a thorough evaluation of various possible modes of ¹⁸O exchange in compound **1**. These are discussed in detail elsewhere.²⁶ The BPR mechanism could be operating, for example, and the pseudorotation step, presumably a fairly high-energy process, could be occurring after rate-limiting hydration and not be seen. Another possibility is that turnstile rotation,^{8,9} the recently proposed alternative to Berry pseudorotation, is in this case providing the means by which the hydroxy ligands of **1b** undergo positional exchange. While a single TR process,

(36) This is an important requirement for phosphoranes to be used as models for investigation of postulated stereomutation mechanisms which are based on an ideal trigonal-bipyramidal geometry. If the phosphorane appears to be strained as a trigonal bipyramid, it may exist in an irregular pentacoordinated geometry. Such geometries have been found in X-ray diffraction studies of strained spiroposphoranes [M. Eisenhut, R. Schmutzler, and W. S. Sheldrick, *J. Chem. Soc. D*, 144 (1973)]. It would be ill-advised to interpret observed stereomutation in such systems in terms of either BPR or TR, both of which assume ground state trigonal-bipyramidal geometries [see P. Meakin, E. L. Muertterties, and J. P. Jesson, *J. Amer. Chem. Soc.*, **94**, 5271 (1972)].

permutationally equivalent to a simple Berry pseudorotation, gives the same unfavorable phosphorane **1e**, a multiple turnstile rotation³⁷ could give phosphorane **1g**, energetically equivalent to **1b** but with ¹⁸O in an apical leaving position, without passing through strained intermediates (see Scheme IV).

By a series of small angle deformations **1b** becomes the turnstile species **1d**, in which the three phosphorus-carbon bonds are mutually 90° from one another and the two hydroxy ligands have been shifted about 9° (while remaining in the same plane) toward the methylene bridge of the bicyclic system. Internal rotation of 180° of the pair of hydroxy ligands, against the trio of ligands defined by the bicyclic system, gives an energetically equivalent turnstile species which can collapse to phosphorane **1g**. Apical loss of the oxo ligand gives an overall isotope exchange which does not involve any strained intermediates.

Examples which demonstrate unequivocal turnstile rotation, single or multiple, are rare, but this must be expected, given its permutational equivalence to BPR.

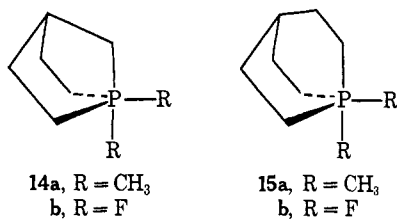
Conclusions

While the oxygen-exchange kinetics in this study do not indicate unequivocally the mode of ¹⁸O exchange in **1**, a real possibility exists that multiple turnstile rotation³⁷ is providing the energetically favored pathway. Certainly there is every indication that further research with compounds **1** and **2**, and similar bridgehead phosphorus systems, will prove critical in the ongoing controversy over such processes.

Independent quantum mechanical calculations by

(37) Another possibility is that the proposed tetragonal pyramid along the pathway of Berry pseudorotation can be so long-lived under some circumstances that by slight angular distortions, it can change into a different tetragonal pyramid, thereby avoiding energetically unfavorable trigonal bipyramids as true intermediates. Thus, in Scheme IV, the **1b** → **1g** conversion could take place without formation of trigonal bipyramid **1e**. This process would be permutationally equivalent to a multiple turnstile rotation discussed below, but distinguishable from either a simple Berry pseudorotation or turnstile rotation. We are indebted to Professor F. H. Westheimer for this suggestion.

Ugi⁸⁰ and by Hoffmann³⁸ predict that, while turnstile rotation is possible, it is expected to demand slightly more energy than Berry pseudorotation. Proton nmr studies on **14a** should demonstrate conclusively whether or not ligand exchange³⁹ is a favorable process in phosphoranes derived from **1**, but the expected instability of **15a**⁴⁰ makes this a less than ideal experiment. Synthesis of **14b** and **15b**, however, both of which should be



reasonably stable compounds, should provide a means toward measuring (by temperature-dependent ¹⁹F nmr spectroscopy)²⁸ the relative abilities of phosphoranes derived from **1** and **2** to undergo positional exchange. While simple Berry pseudorotation is expected to transpire unfettered in **15b**, there is good reason to believe that the analogous process would be significantly disfavored in **14b**; on the other hand, if multiple turnstile rotational processes are possible in these systems, no great difference in the facility of positional interchange in **14b** and **15b** is expected.

Experimental Section

Materials. Compounds 1-5 were prepared as described in the previous paper.¹⁰ Triethylphosphine oxide (**6**) was purchased from K & K Labs., Inc., Hollywood, Calif. Kimax color-break 1-ml ampoules of N-51A borosilicate glass were purchased from Kimble Products (Owens, Ill.), Toledo, Ohio. These ampoules, used for kinetics in acid and neutral solution, were stable when filled with a 1-ml solution of phosphine oxide, even at 152°. Kinetics in basic solution were followed in brass-enclosed Teflon containers fitted with a Teflon plug which was secured by a threaded brass top, as described by Eberhard.⁴¹ Nonnormalized 90% ¹⁸O-enriched water was purchased from Miles Labs., Elkhart, Ind. A solution of DCl (20%) in D₂O was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis.

Preparation of ¹⁸O-Labeled Phosphine Oxides 1-6. Labeled phosphine oxides were prepared by heating 50-100 mg of oxide at 100° for 2-7 days in ¹⁸O-enriched water which had been made acidic (1-5 N HCl) by bubbling dry HCl gas into the water, with cooling, for several minutes. The acid-water was removed by high vacuum distillation and recovered in a Dry Ice-acetone trap. The residue was dissolved in 1 ml of water and extracted several times with CHCl₃. The combined organic layers were concentrated and the residue was purified by vacuum sublimation.

Kinetic Methods. The general procedures used were as described by Gorenstein.³ Phosphine oxides were recovered from aqueous medium, dissolved in CHCl₃, and analyzed for per cent ¹⁸O by monitoring the absorbances of phosphoryl bands in spectra obtained on a Perkin-Elmer Model 421 spectrophotometer. One run for each compound was checked by determining the per cent ¹⁸O of selected points by monitoring the M and M + 2 ions on mass spectra measured by a Consolidated Model 21-103C spectrometer.

(38) R. Hoffmann, J. M. Howell, and E. L. Muetterties, *J. Amer. Chem. Soc.*, **94**, 3047 (1972).

(39) C. H. Bushweller, H. S. Bilofsky, E. W. Turnblom, and T. J. Katz, *Tetrahedron Lett.*, 2401 (1972).

(40) E. W. Turnblom and T. J. Katz, Jr., *J. Amer. Chem. Soc.*, **95**, 4292 (1973).

(41) A. Eberhard, Ph.D. Thesis, Harvard University, 1964, p 73.

Compounds 4-6 gave unambiguous spectra from which the per cent ¹⁸O could be determined from relative absorbances of the ¹⁸O=P and ¹⁶O=P bands. The best procedure for compound **3**, which gave more complicated spectra presumably due to Fermi resonance,¹⁰ was to follow the 1157-cm⁻¹ band for ¹⁸O=P and the 1205-cm⁻¹ band for ¹⁶O=P. Spectra of compound **1** were even more complicated, again attributed to Fermi resonance.¹⁰ The best procedure for this compound was to follow the 1144-cm⁻¹ band for ¹⁸O=P and the 1178-cm⁻¹ band for ¹⁶O=P.

The quality of the least-squares fits for the pseudo-first-order kinetic run and proximity of rate constants obtained to those determined by mass spectrometry were the criteria used for finding the best procedure for spectral analysis in each case. All methods tried were satisfactory for preparation of pH-rate profiles, but it was desirable to find the best possible procedures for determination of activation parameters and solvent-isotope effects.

Pseudo-first-order rate constants were converted to second-order rate constants, and corrected for thermal expansion of water at the same time, by dividing by the concentration of catalyst corrected for expansion of water.⁴² These corrected values were used in the determination of activation parameters. Solvent isotope effect studies were determined as follows: phosphine oxides of exactly the same per cent ¹⁸O incorporation were dissolved in either 0.475 N HCl in H₂O or 0.475 N DCl in D₂O, and these solutions, in glass ampoules, were simultaneously heated at 101°. Points for D₂O and H₂O were taken at the same intervals. This eliminated the complication of possible temperature fluctuation and utilized to full advantage the excellent precision of the infrared spectrometer.

Eight of the points on the pH-rate profiles in Figure 1 are extrapolations of one of two kinds. The points for compounds **4** and **6** in 0.10 N HCl and for compound **1** in 0.01 N HCl are derived from a plot of log *k* vs. 1/*T* for each compound; the points for compounds **4**, **5**, and **6** in 0.05 N phosphate buffer, and for compounds **5** and **6** in 1.00 N KOH, were estimated from rates determined at higher temperatures by using ratios of other compounds (whose rates at both the higher temperature and 101° were conveniently measured). It was felt that while this latter method left something to be desired, it was, however, a shade better than using the generally applied approximation of a factor of 10 for every 25° difference in rate (based on Arrhenius).

Computer Programs. First-order rate constants were calculated by LLS, a general linear least-squares program.⁴³ Activation parameters were computed by ACTENG, a least-squares program which calculates Δ*H*[‡] and Δ*S*[‡] values valid only for the middle of the temperature range over which rate constants are submitted.⁴³

Acknowledgments. Financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the U. S. Public Health Service, Grant AM-13529, is gratefully acknowledged. We thank Dr. E. Gordon for help with the computer programs, and Dr. B. Bartman for help with general kinetic procedures. We also wish to thank Professor D. S. Noyce for helpful discussions.

Supplementary Material Available. A table showing kinetic data for oxygen-18 exchange of phosphine oxides 1-6 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-5199.

(42) "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p F4.

(43) D. F. DeTar and C. E. DeTar, "Computer Programs for Chemistry," Vol. III, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1969, Chapter 2.